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Le et al.

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(54) **RECOMBINANT A2-SPECIFIC TNF $\alpha$  SPECIFIC ANTIBODIES**

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(57) **ABSTRACT**

Anti-TNF antibodies, fragments and regions thereof which are specific for human tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) and are useful in vivo diagnosis and therapy of a number of TNF $\alpha$ -mediated pathologies and conditions, as well as polynucleotides coding for murine and chimeric antibodies, methods of producing the antibody, methods of use of the anti-TNF antibody, or fragment, region or derivative thereof, in immunoassays and immunotherapeutic approaches are provided.

(51) **Int. Cl.**

*A61K 39/395* (2006.01)  
*C07K 16/28* (2006.01)

(52) **U.S. Cl.** ..... 424/145.1; 424/130.1; 424/133.1; 424/141.1; 530/387.1; 530/387.3; 530/388.1; 530/388.23

(58) **Field of Classification Search** ..... 464/130.1, 464/145.1; 530/387.1, 388.23

See application file for complete search history.

22 Claims, 37 Drawing Sheets

**EXHIBIT**

tables

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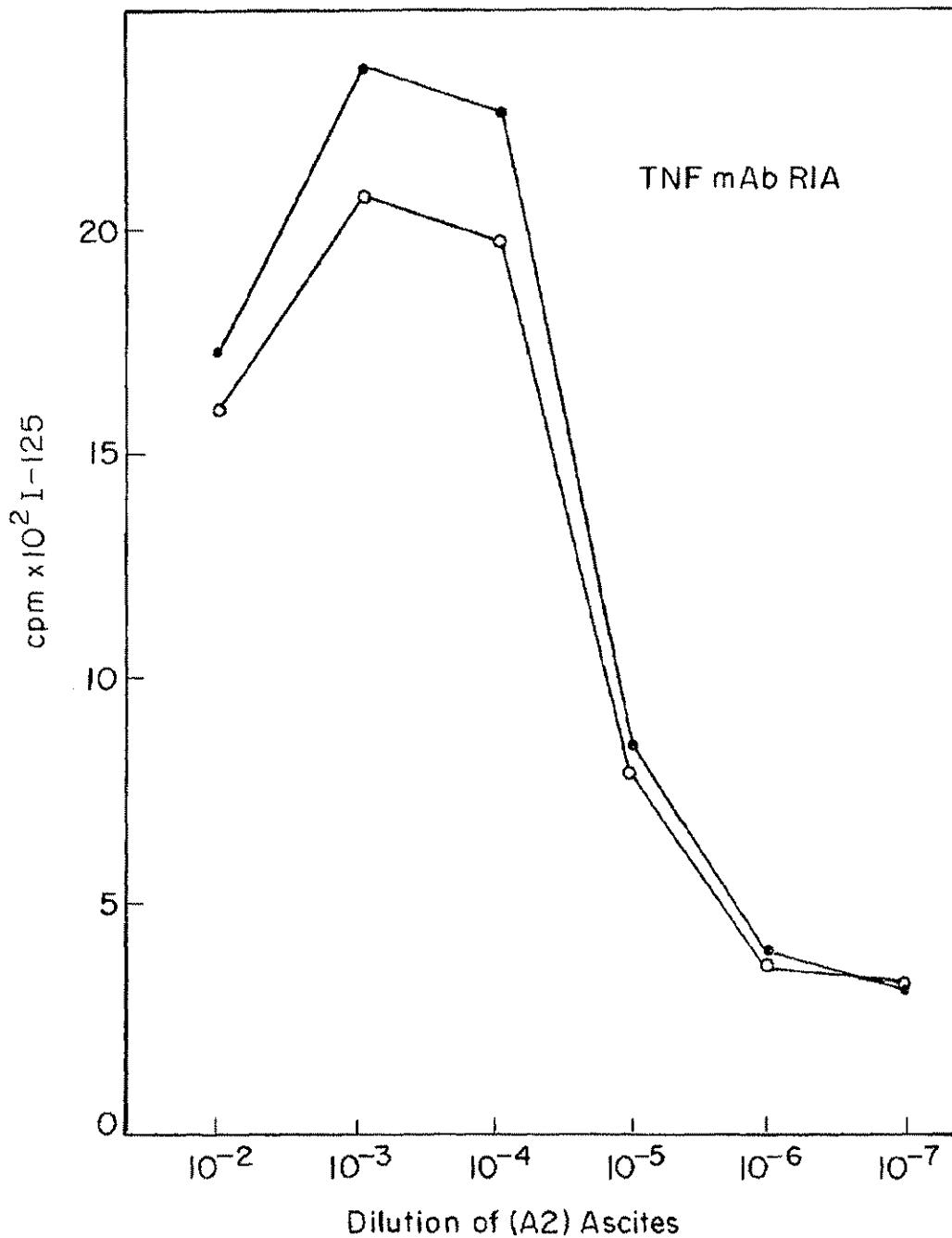


FIG. 1

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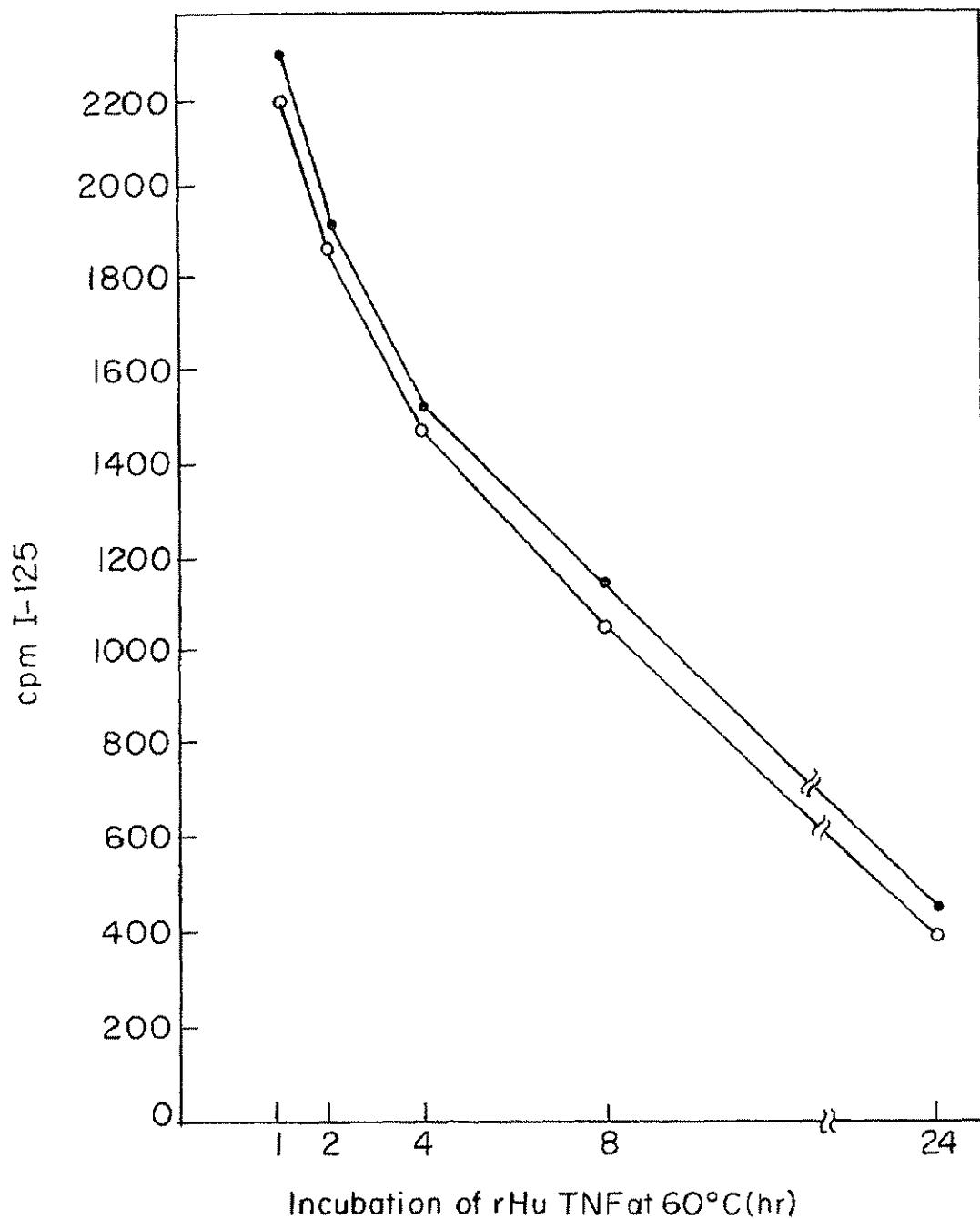


FIG. 2

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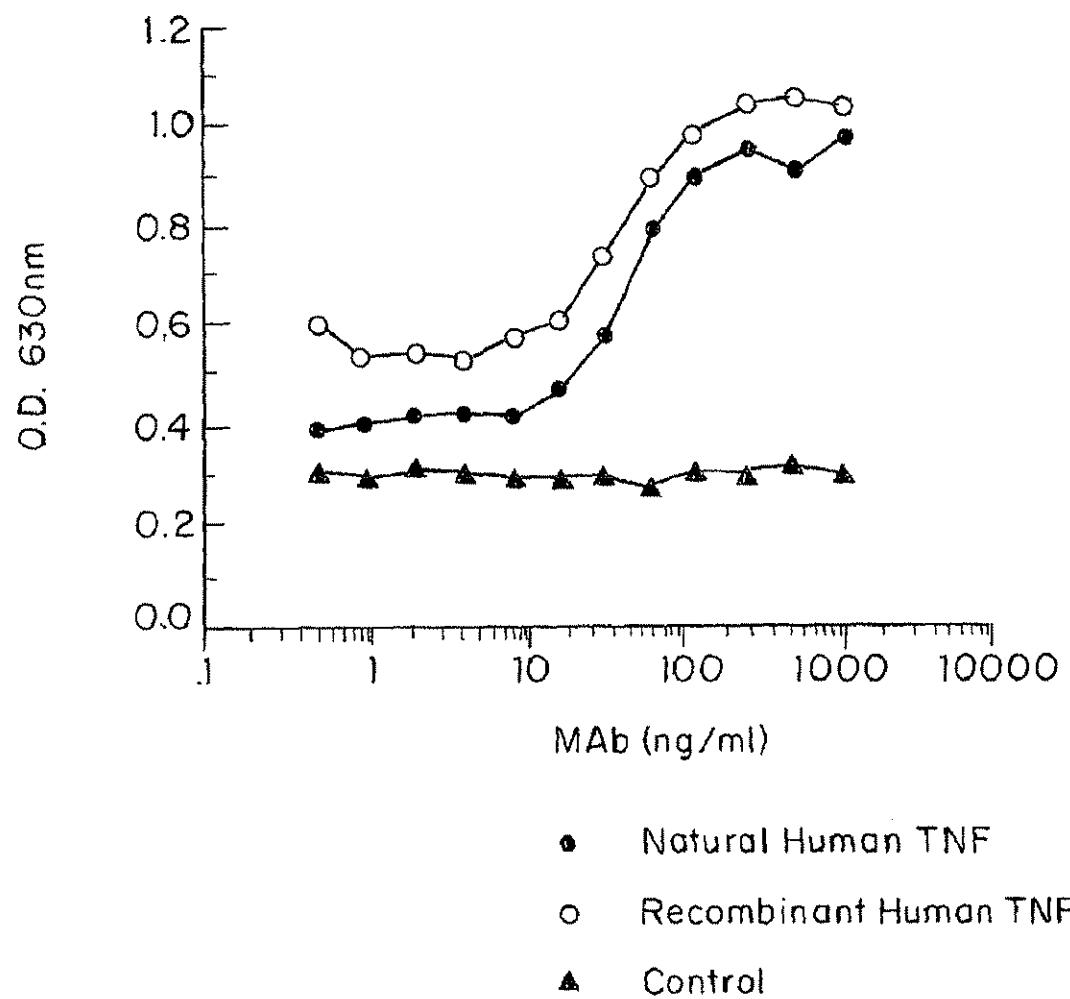


FIG. 3

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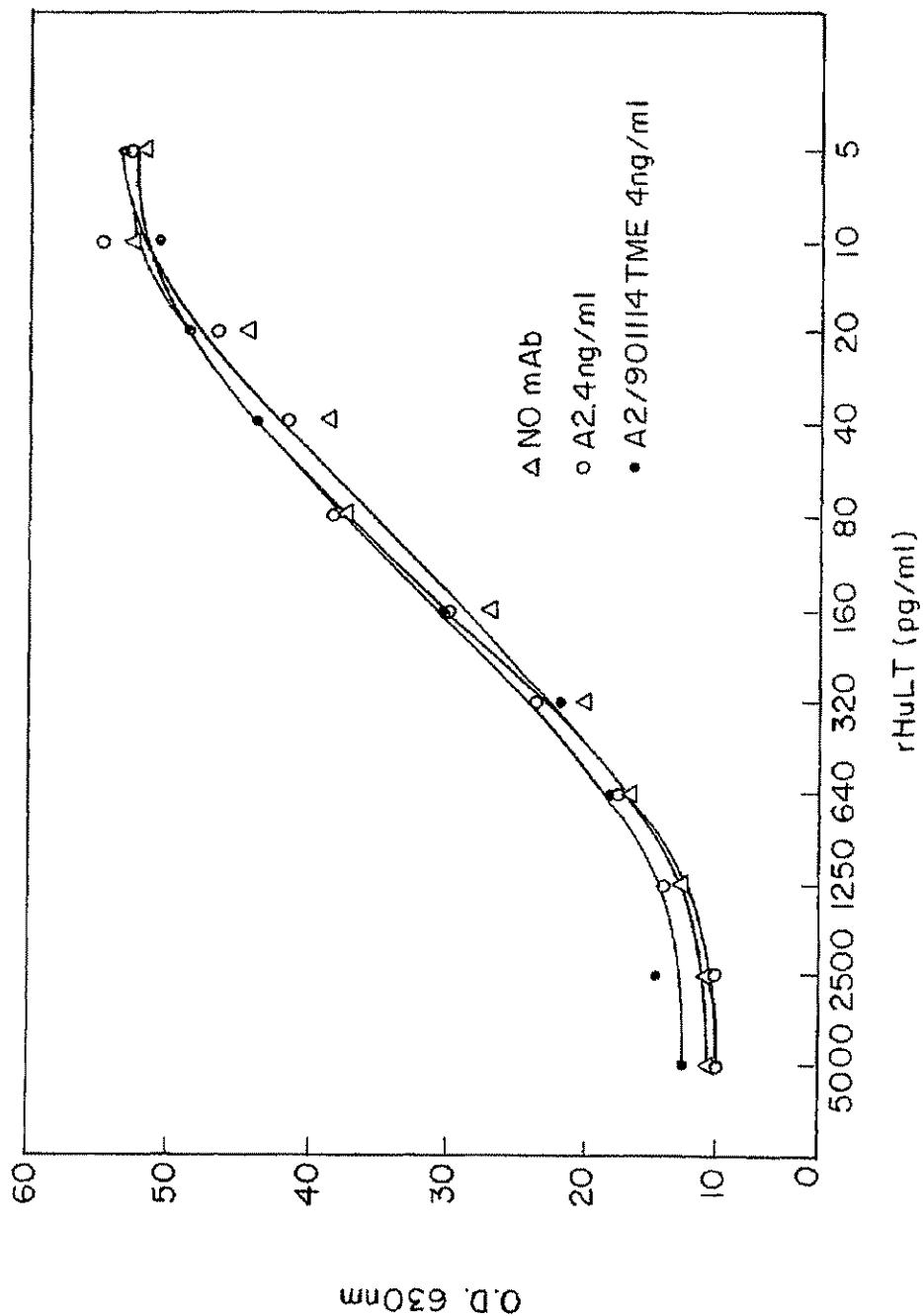


FIG. 4

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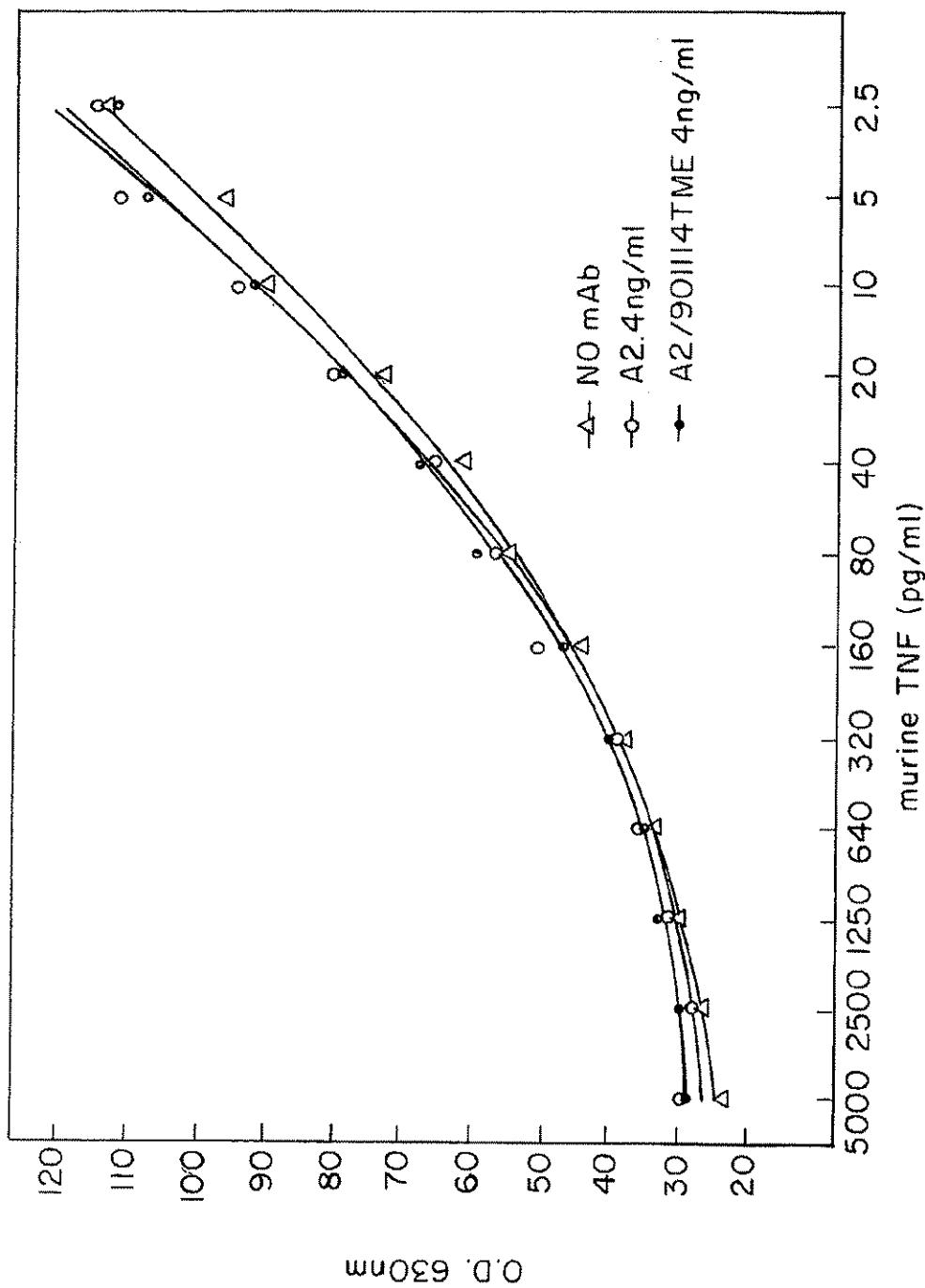


FIG. 5

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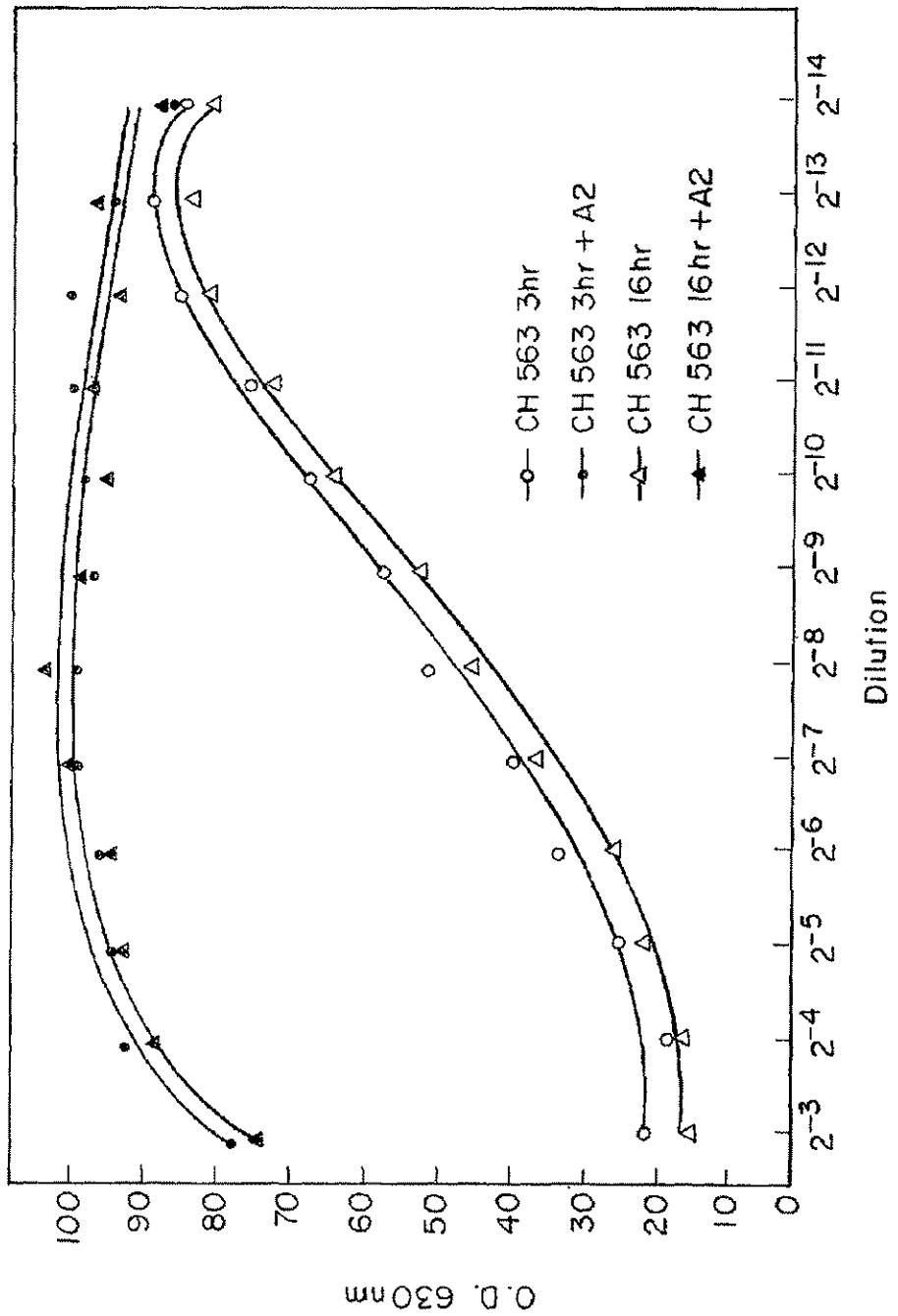


FIG. 6

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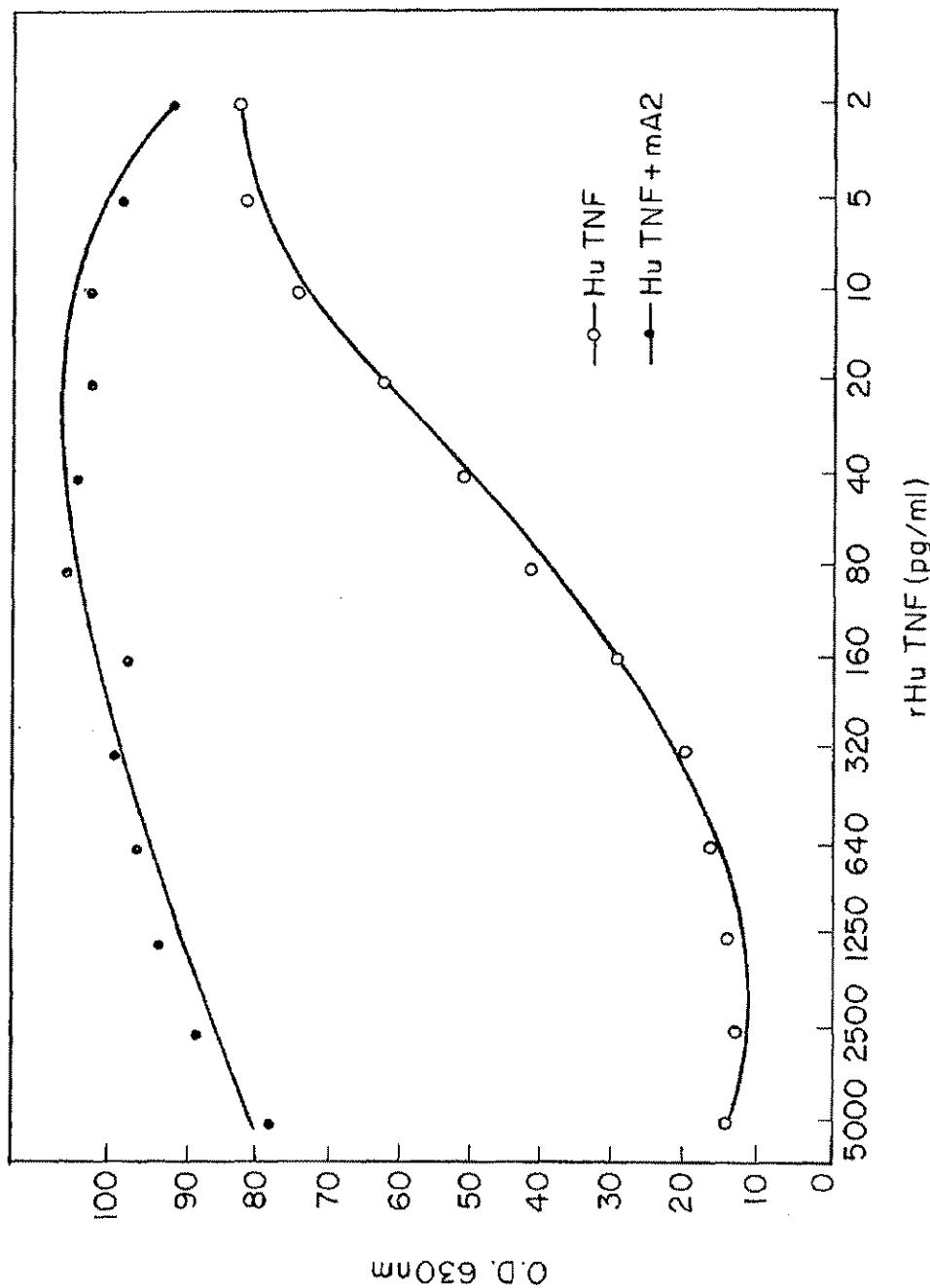


FIG. 7

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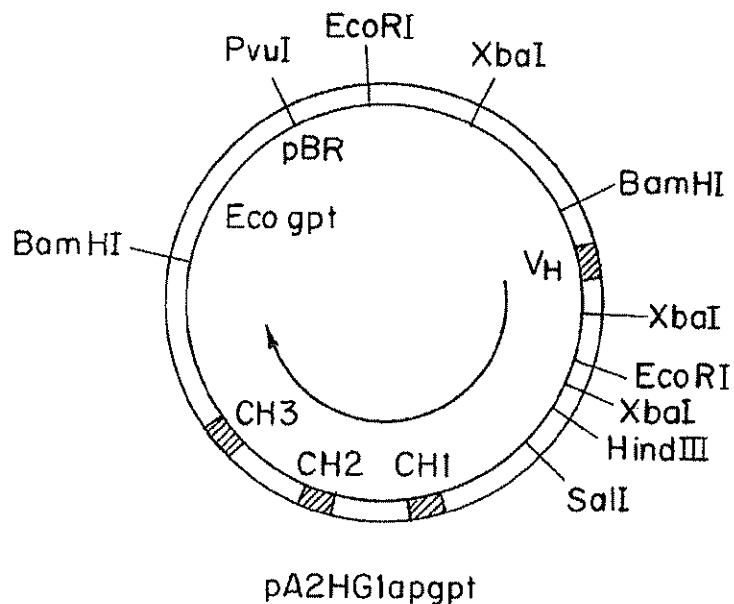


FIG. 8A

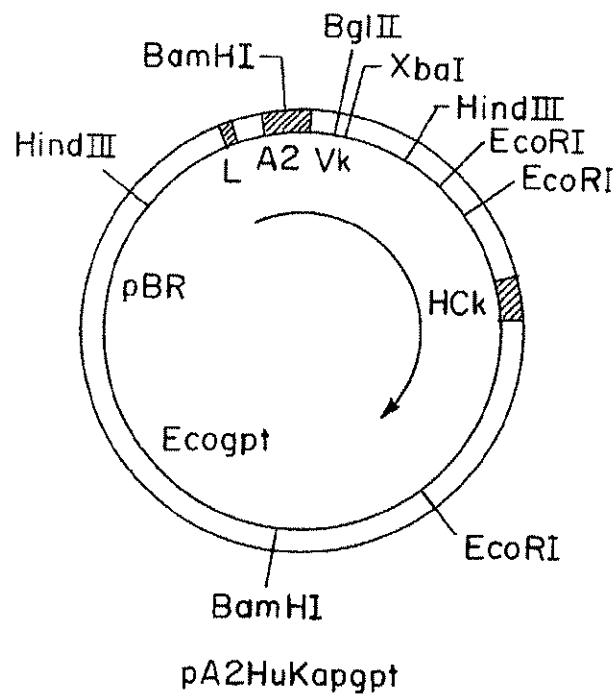


FIG. 8B

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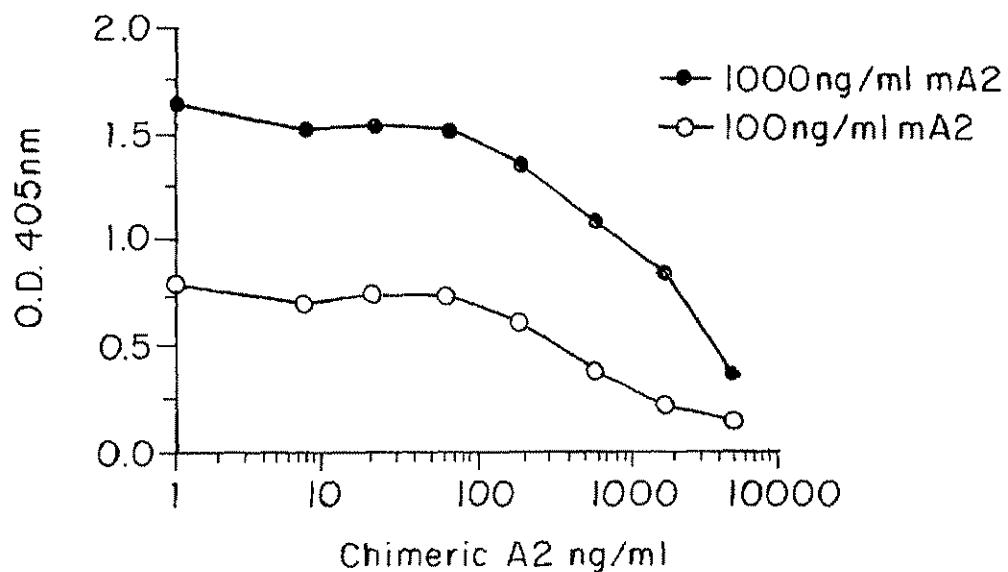


FIG. 9A

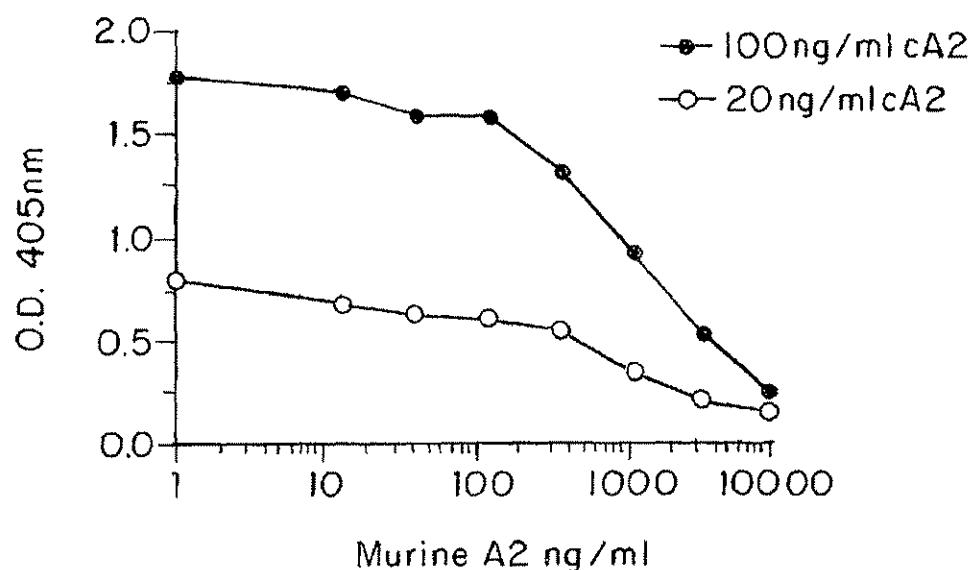


FIG. 9B

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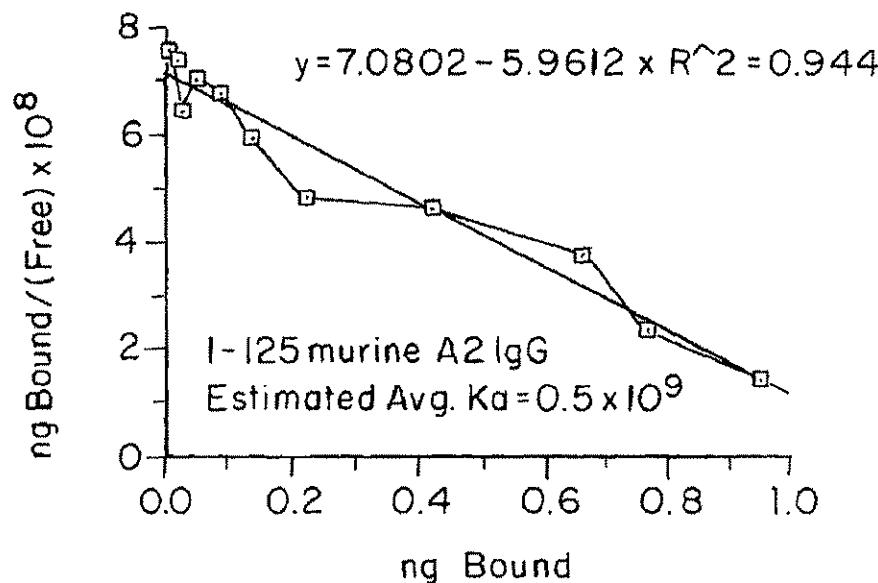


FIG. 10A

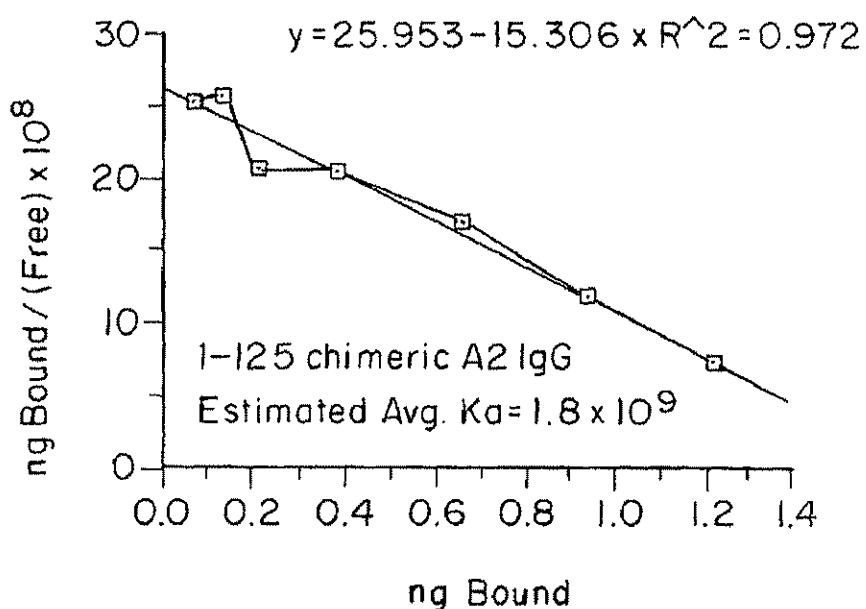


FIG. 10B

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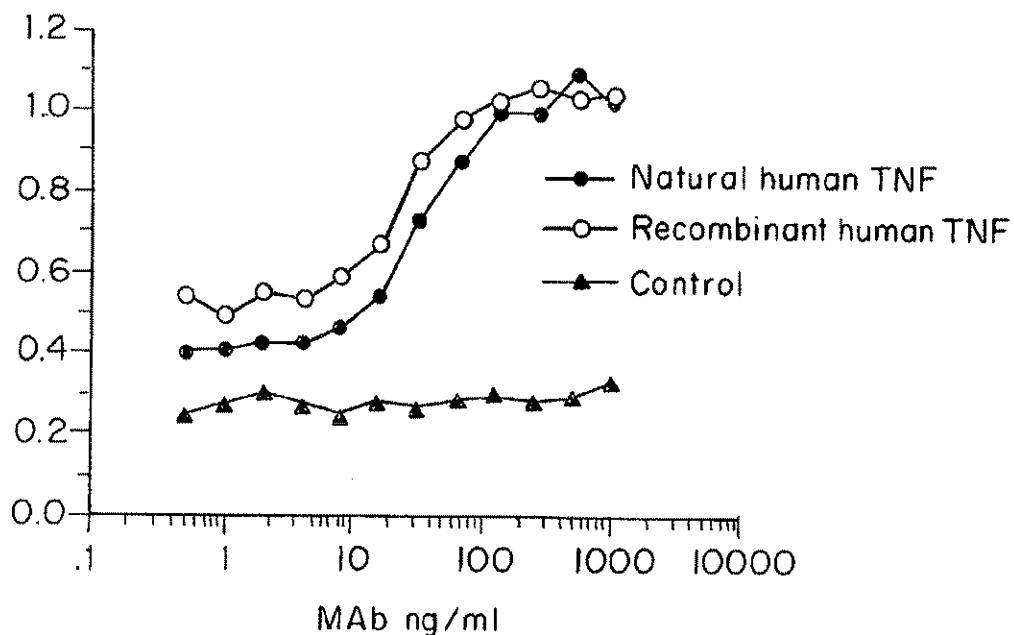


FIG. 11

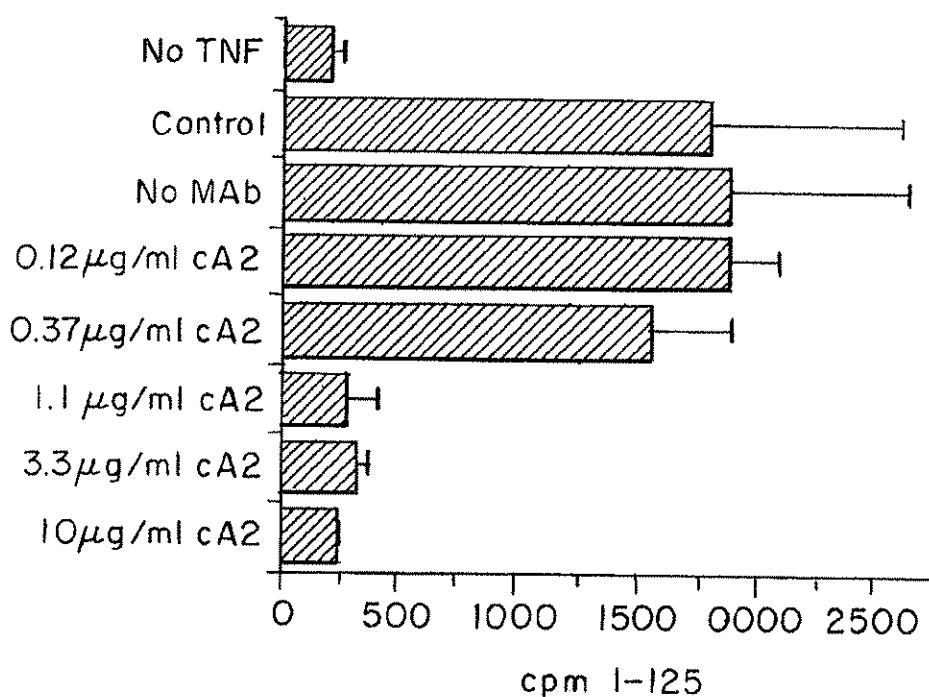


FIG. 12

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1 Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro  
21 Gln Ala Glu Gly Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu Leu Ala Asn Gly  
41 Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser Glu Gly Leu Tyr Leu Ile Tyr Ser  
61 Gln Val Leu Phe Lys Gly Gln Gly Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile  
81 Ser Arg Ile Ala Val Ser Tyr Gln Thr Lys Val Asn Leu Leu Ser Ala Ile Lys Ser Pro  
101 Cys Gln Arg Glu Thr Pro Glu Gly Ala Glu Ala Lys Pro Trp Tyr Glu Pro Ile Tyr Leu  
121 Gly Gly Val Phe Gln Leu Glu Lys Gly Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp  
141 Tyr Leu Asp Phe Ala Glu Ser Gly Gln Val Tyr Phe Gly Ile Ile Ala Leu  
150

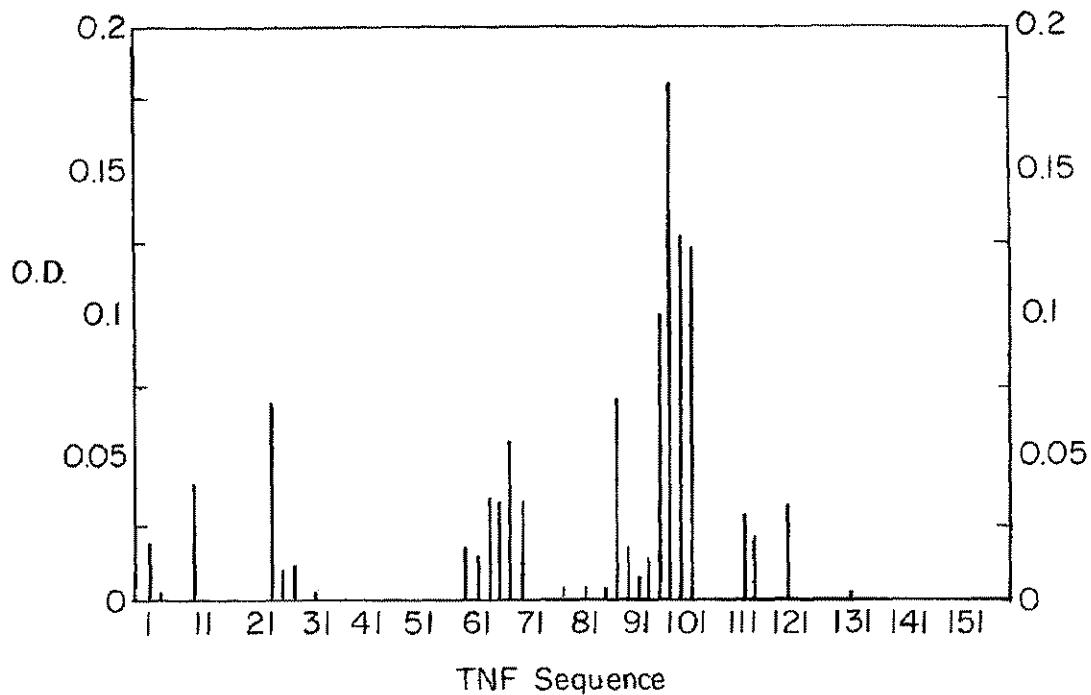
FIG. 13

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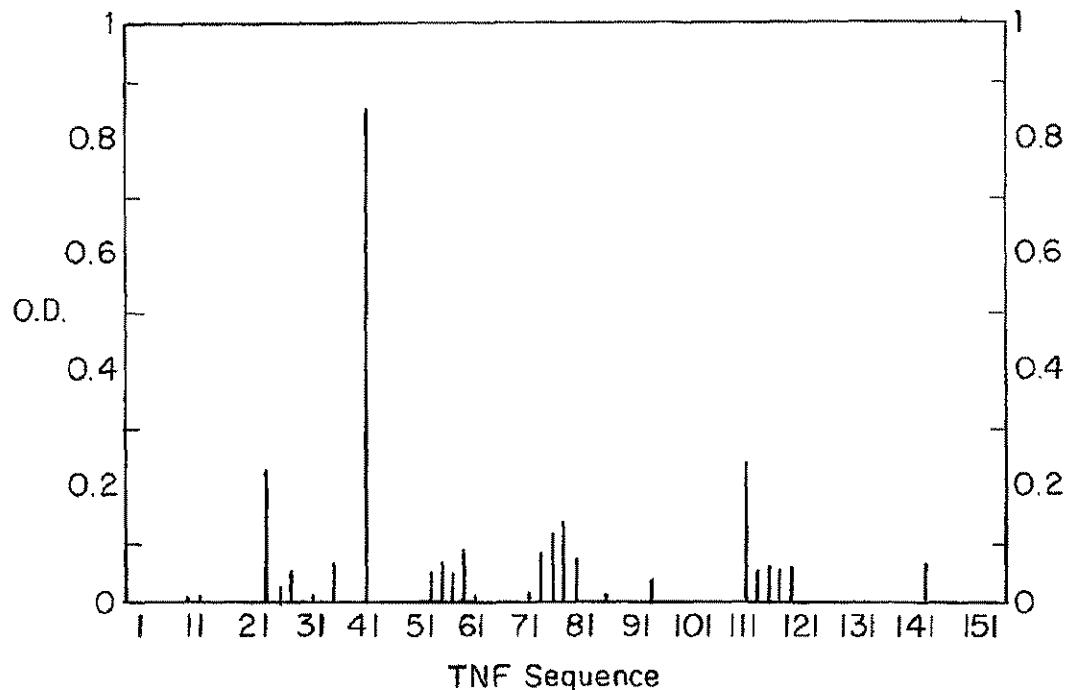
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**FIG. 14A**



**FIG. 14B**

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1	Val Arg Ser Ser Ser Arg Thr Pro Ser Asp Lys Pro Val Ala His Val Val Ala Asn Pro
21	Gln Ala Glu GLY Gln Leu Gln Trp Leu Asn Arg Arg Ala Asn Ala Leu Leu Ala Asn Gly
41	Val Glu Leu Arg Asp Asn Gln Leu Val Val Pro Ser Glu GLY Leu Tyr Leu Ile Tyr Ser
61	Gln Val Leu Phe Lys GLY Gln GLY Cys Pro Ser Thr His Val Leu Leu Thr His Thr Ile
81	Ser Arg Ile Ala Val Ser Tyr Gln Thr Lys Val Asn Leu Ser Ala Ile Lys Ser Pro
101	Cys Gln Arg Glu Thr Pro Glu GLY Ala Glu Ala Lys Pro Trp Tyr Glu Pro Ile Tyr Leu
121	GLY GLY Val Phe Gln Leu Glu Lys GLY Asp Arg Leu Ser Ala Glu Ile Asn Arg Pro Asp
141	Tyr Leu Asp Phe Ala Glu Ser GLY Gln Val Tyr Phe GLY Ile Ile Ala Leu
150	
30	
50	
70	
90	
110	

FIG. 15

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GACATCTGCTGACTCAGTCTCCAGCCATCCTGCTGAGTCCAGGAGAAAGACTCAGT  
AspIleLeuIleThrGlnSerProAlaIleLeuSerValSerProGlyGluArgValSer

TTCTCCTGCAGGCCAGTCAGTTCGTTGGCTCAAGCATCCACTGGTATCAGCAAAGAACAA  
PheSerCysArgAlaSerGlnPheValGlySerSerIleHisIleAspGlyGlnArgThr

AATGGTTCTCAAGGCTCTCATAAAGTATGCTTCTGAGTCTATGGATCCCTTCC  
AsnGlySerProArgLeuIleLeuIleLeuIleAspSerGluSerMetSerGlyIleProSer

AGGTTAGTGGCAGTGGATCAGGACAGATTACTCTTAGCATCAACACTGTGGAGTCT  
ArgPheSerGlySerGlySerGlySerGlyThrAspPheThrLeuSerIleAsnThrValGluSer

GAAGATATGCAAGATTACTGTCAAGAAAGTCACGGCATTCACGTTTCCGGCTCG  
GluAspIleAlaAspTyrTyrCysGlnGlnSerHisSerTrpProPheThrPheGlySer

GGGACAAATTGGAAAGTAAAAA  
GlyThrAsnLeuGluValLys

FIG. 16A

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GAAGTGAGCTTGAGGAGTCTGGAGGGCTTGCGAACCTGGAGGATCCATGAAACTC  
GluValLysLeuGluGluSerGlyGlyLeuValGlnProGlyGlySerMetLysLeu  
TCCCTGTGCTCTGGATTCACTTCAGTAACCACTGGATGAACTGGGTCCGCCAGTCT  
SerCysValAlaSerGlyPheIlePheSerAsnHisTrpMetAsnTrpValArgGlnSer  
CCAGAGAAGGGCTTGAGTGGTTGCTGAAATTAGATCAAAATCTTAAATTCTGCAACA  
ProGluLysGlyLeuGluTrpValAlaGluIleArgSerLysSerIleAsnSerAlaThr  
CATTTATGCCGAGTCTGTGAAGGAGGGTTCACCATCTCAAGAGATGATTCCAAAGGTGCT  
HisTyrAlaGluSerValLysGlyArgPheThrIleSerArgAspAspSerLysSerAla  
GTGTACCTGCAAAATGACCGACTTAAGAACACTGAAGACACTGGCGTTATTACTGTTCCAGG  
ValTyrLeuGlnMetThrAspLeuArgThrGluAspThrGlyValTyrTyrCysSerArg  
AATTACTACGGTAGTACGACTACTGGGGCCAAGGCCAACACTCACAGTGTCC  
AsnTyrTyrGlySerThrTyrAspTyrTrpGlyGlnGlyThrThrLeuThrValSer

FIG. 16B

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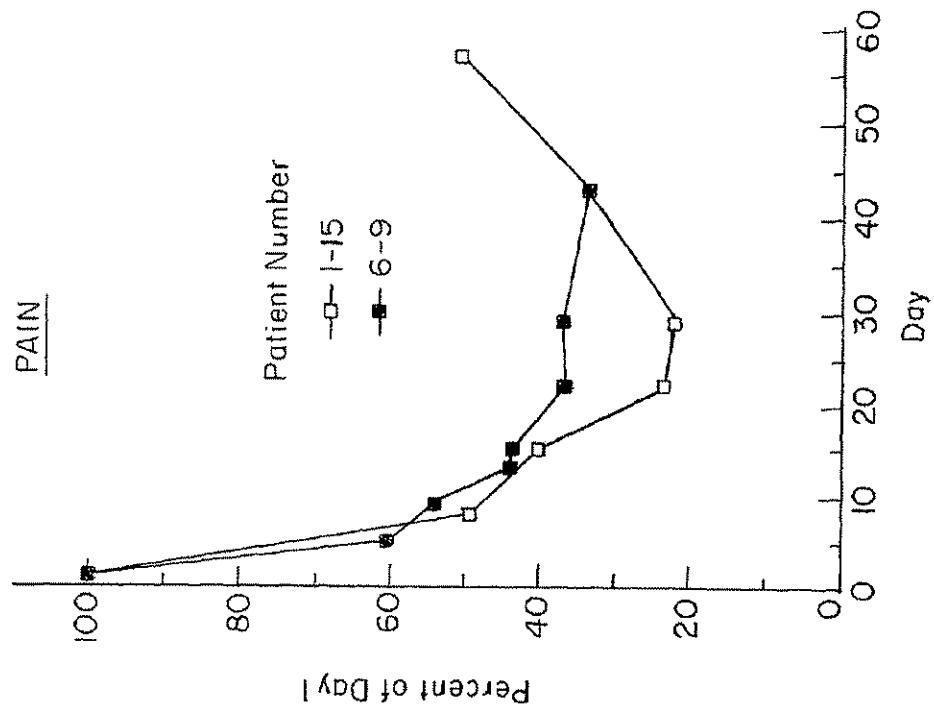


FIG. 18

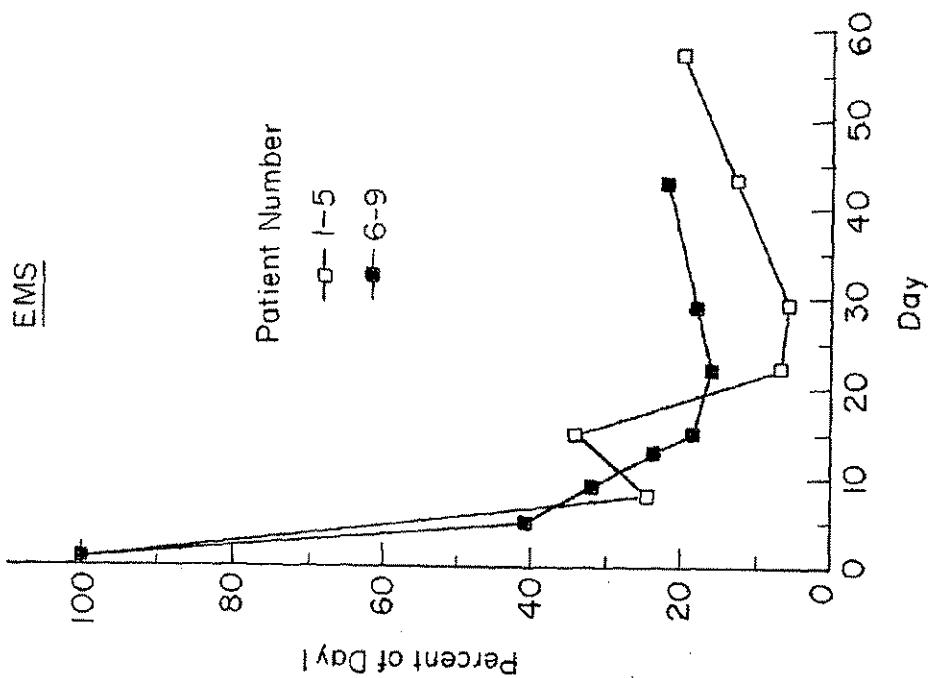


FIG. 17

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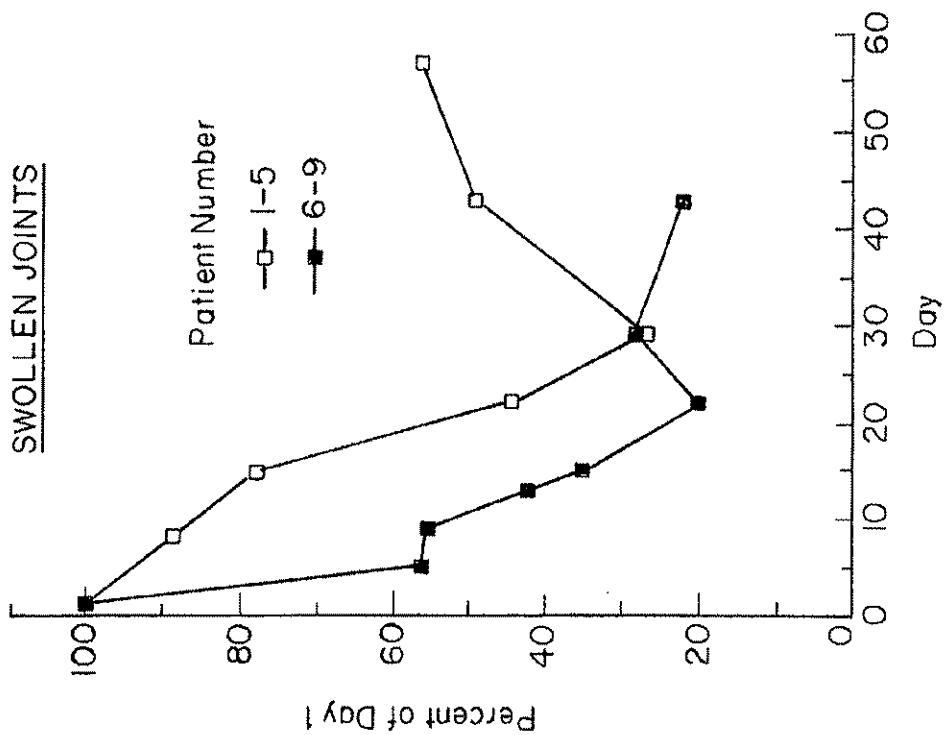


FIG. 20

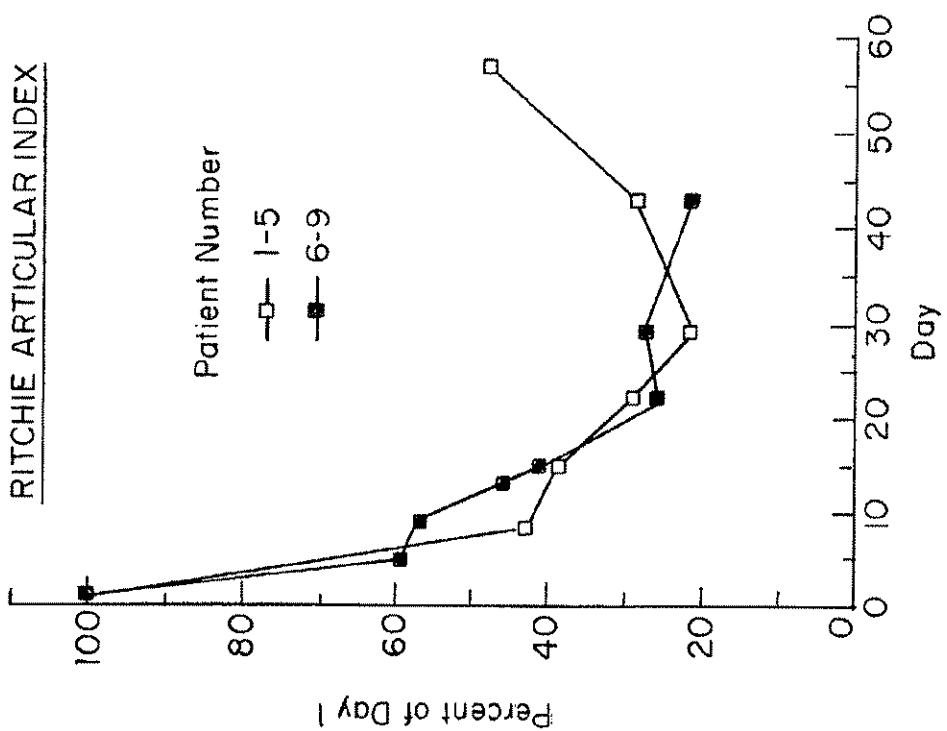


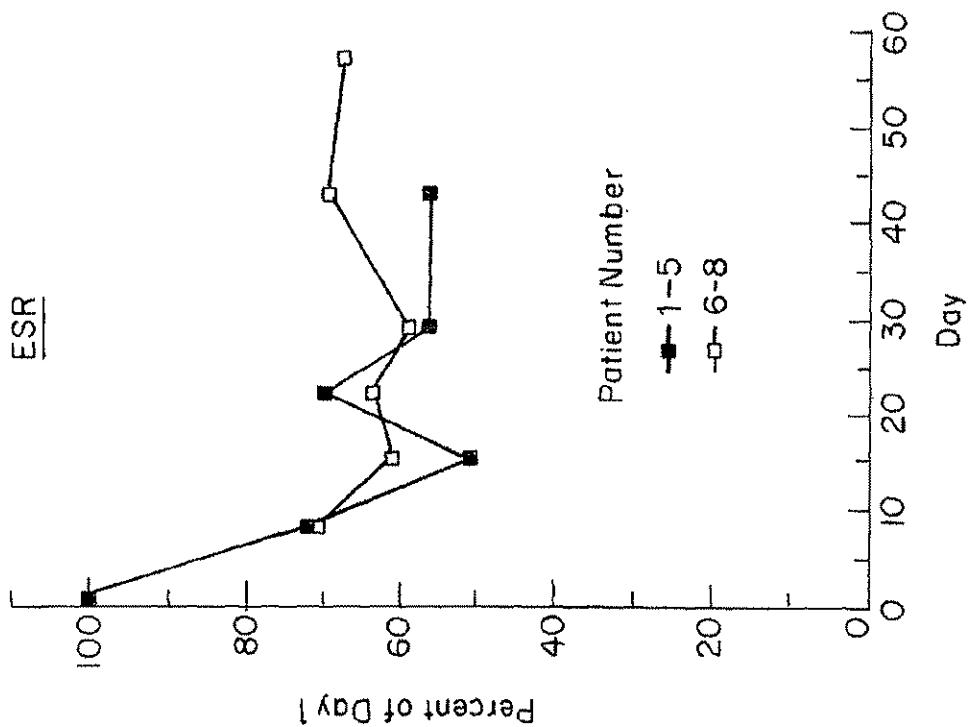
FIG. 19

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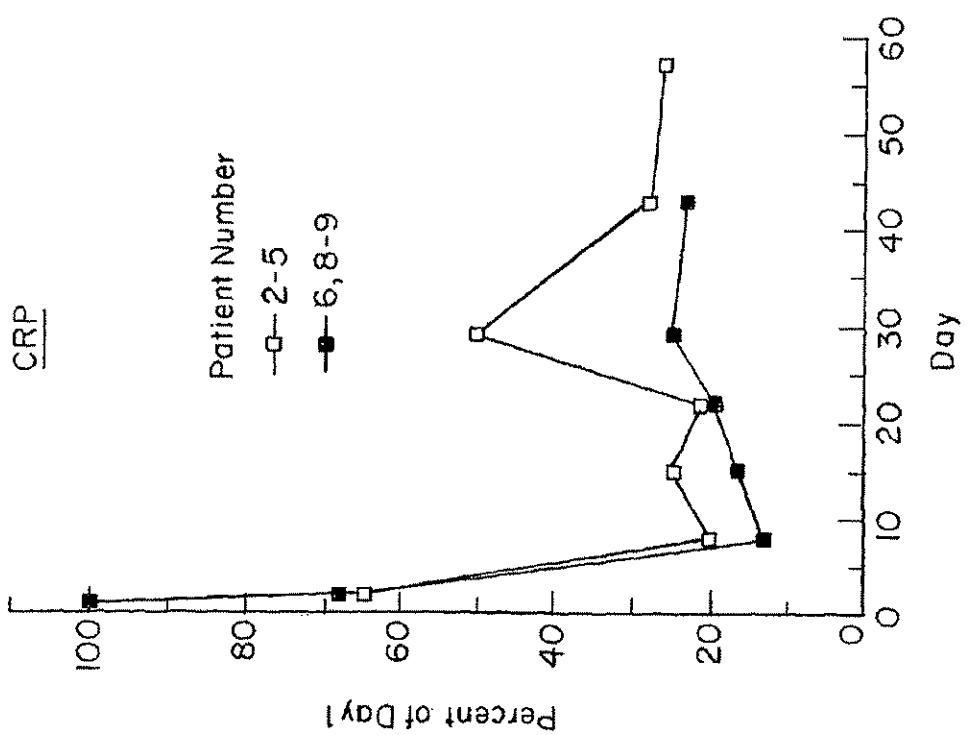
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**FIG. 22**



**FIG. 21**

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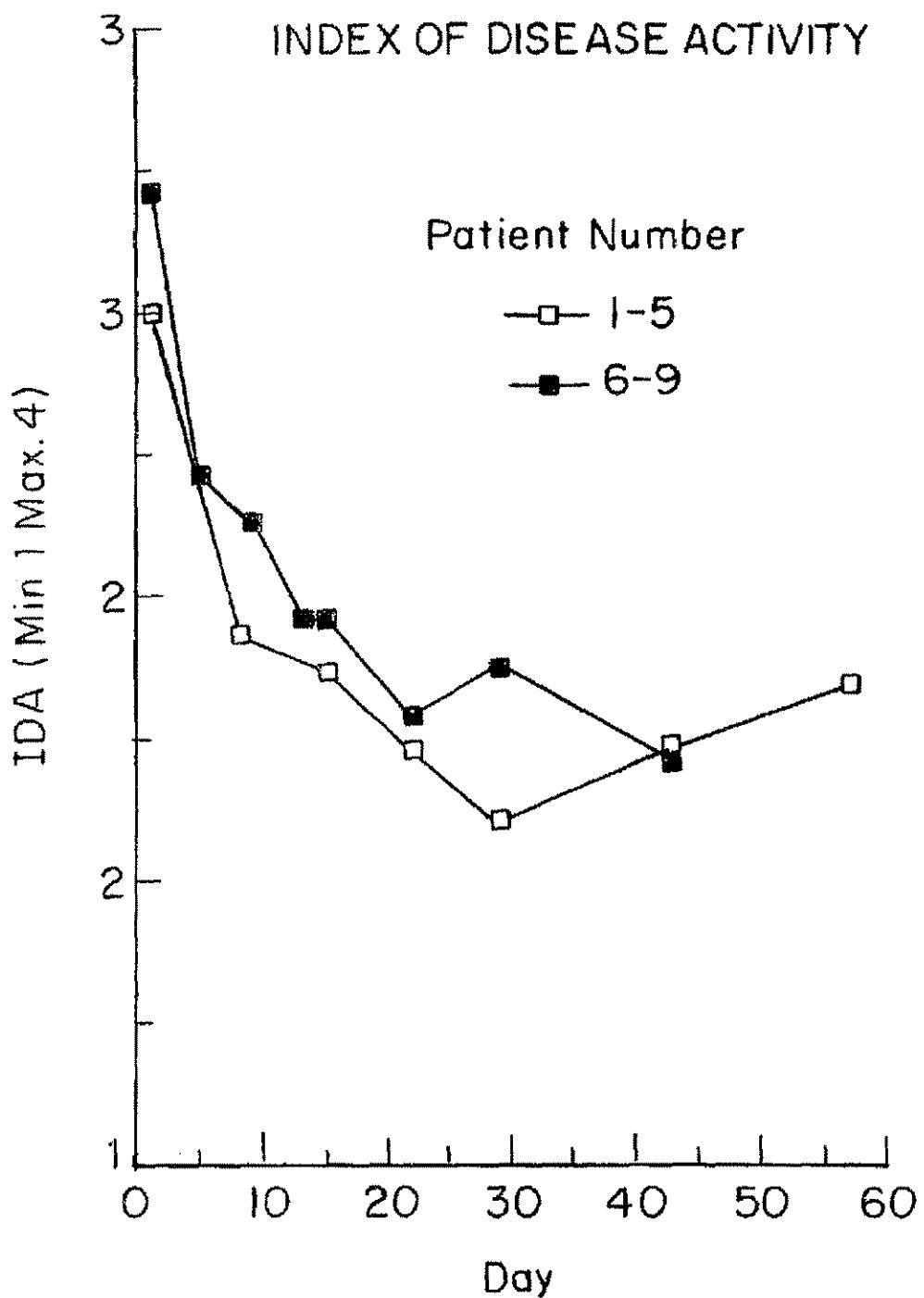


FIG. 23

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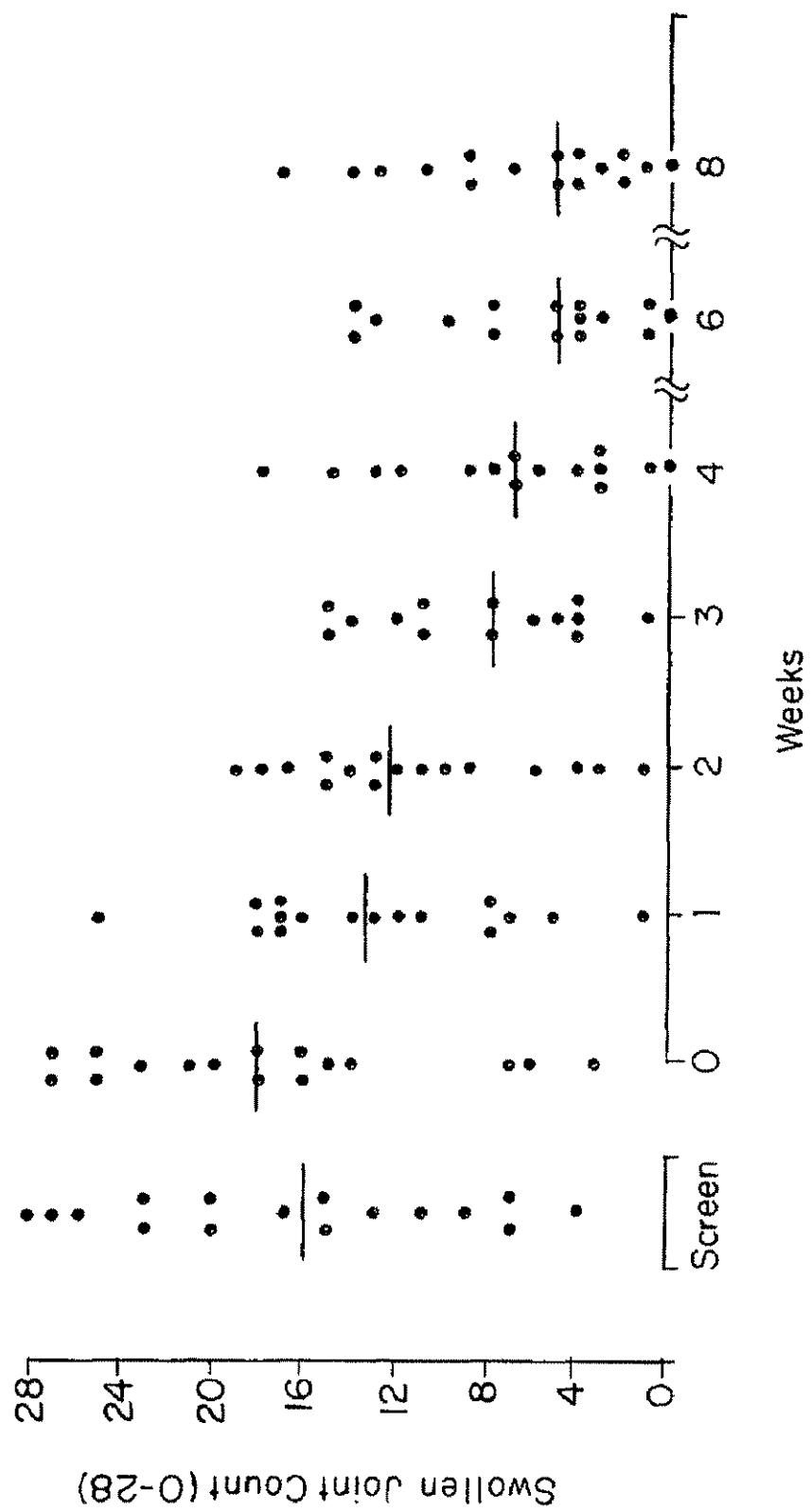


FIG. 24

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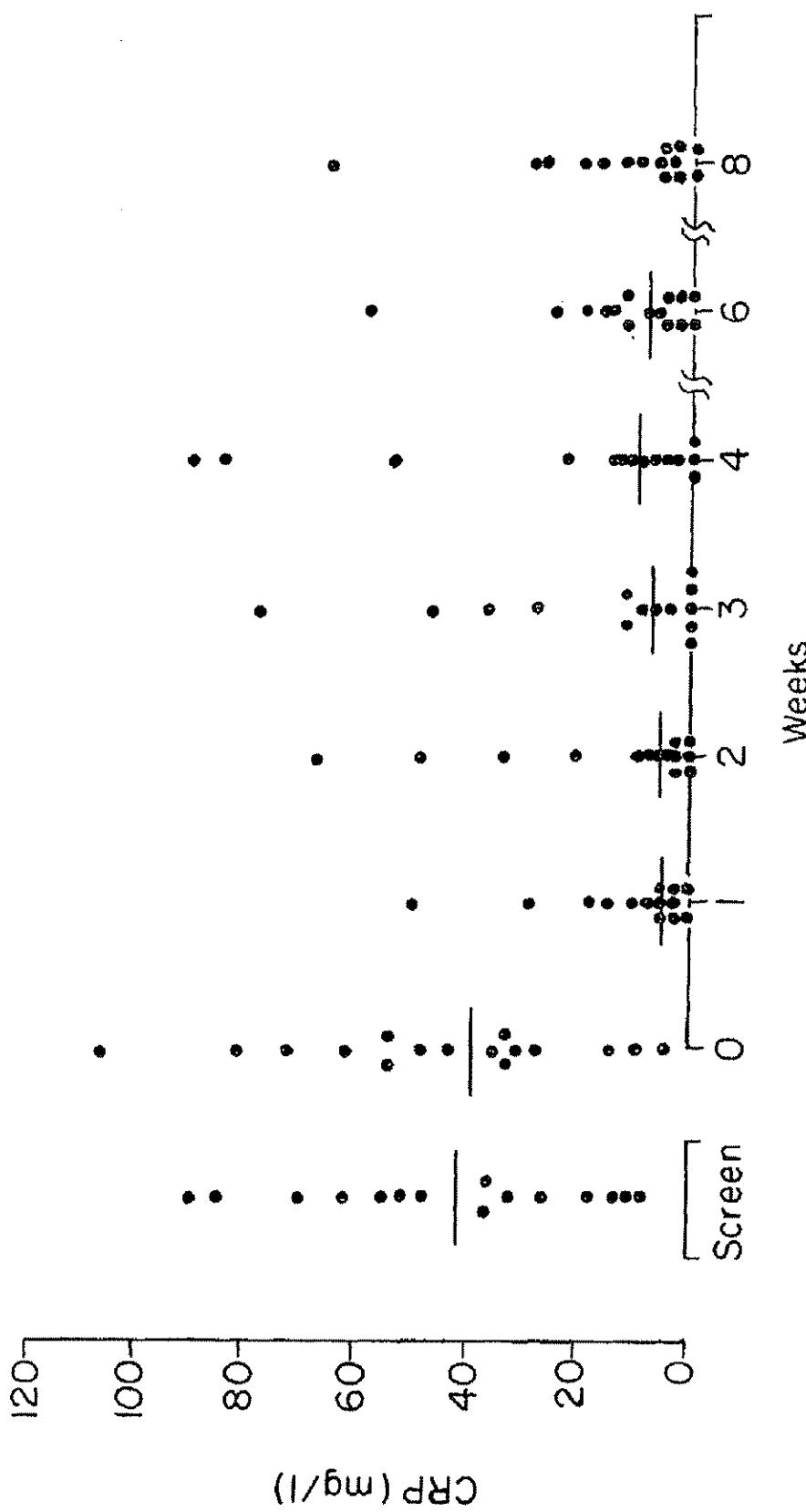


FIG. 25

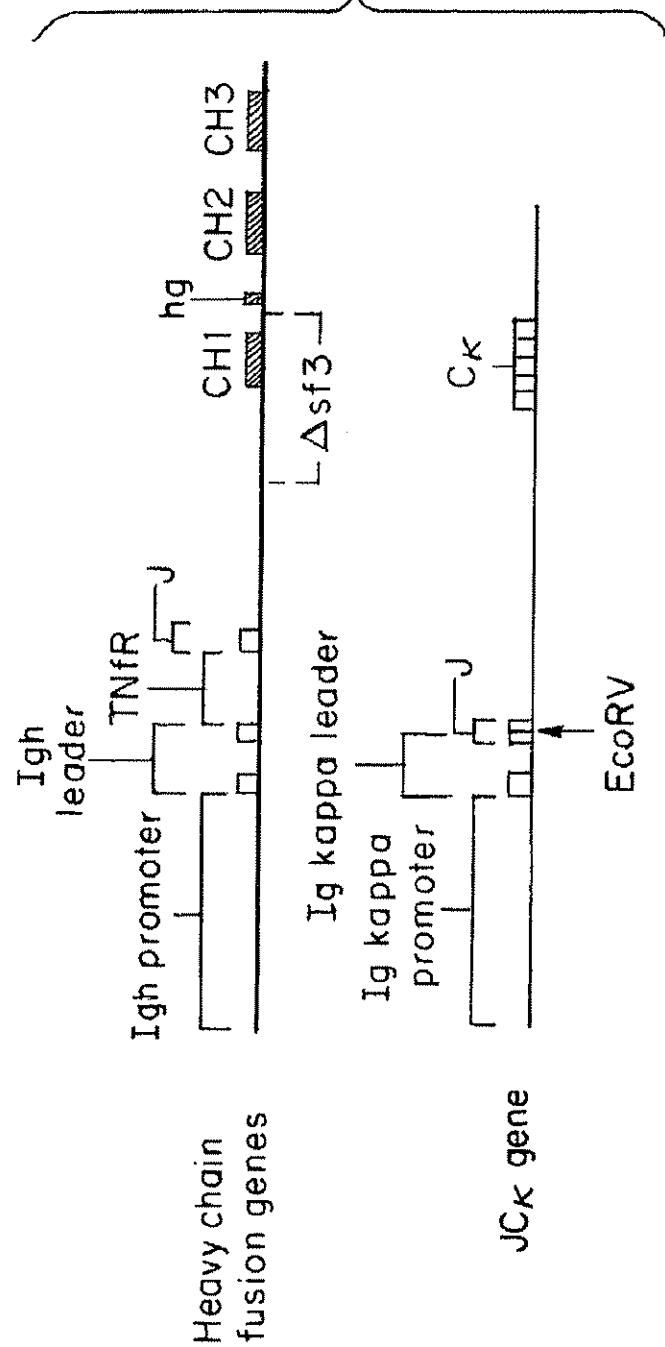
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FIG. 26A



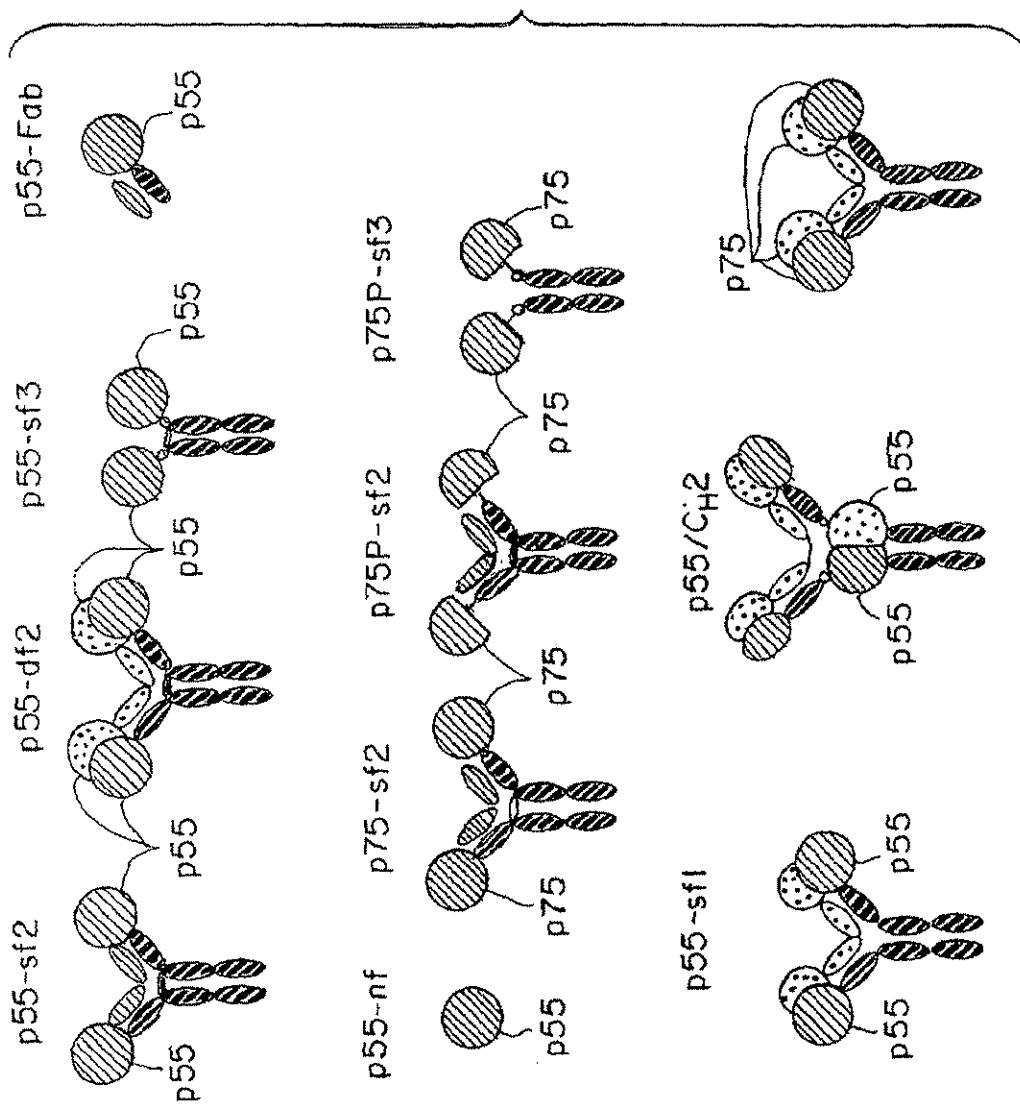
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FIG. 26B



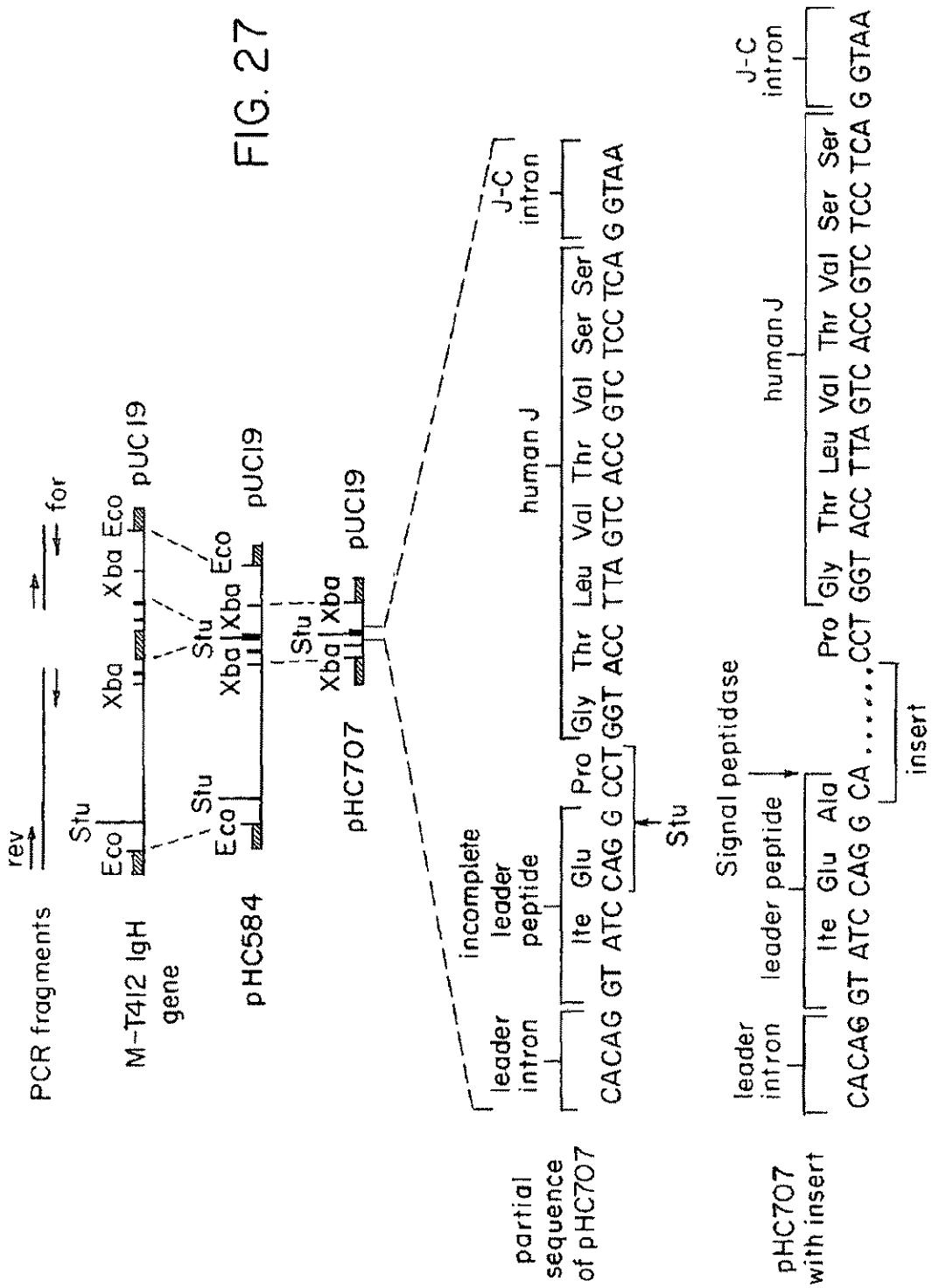
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FIG. 27



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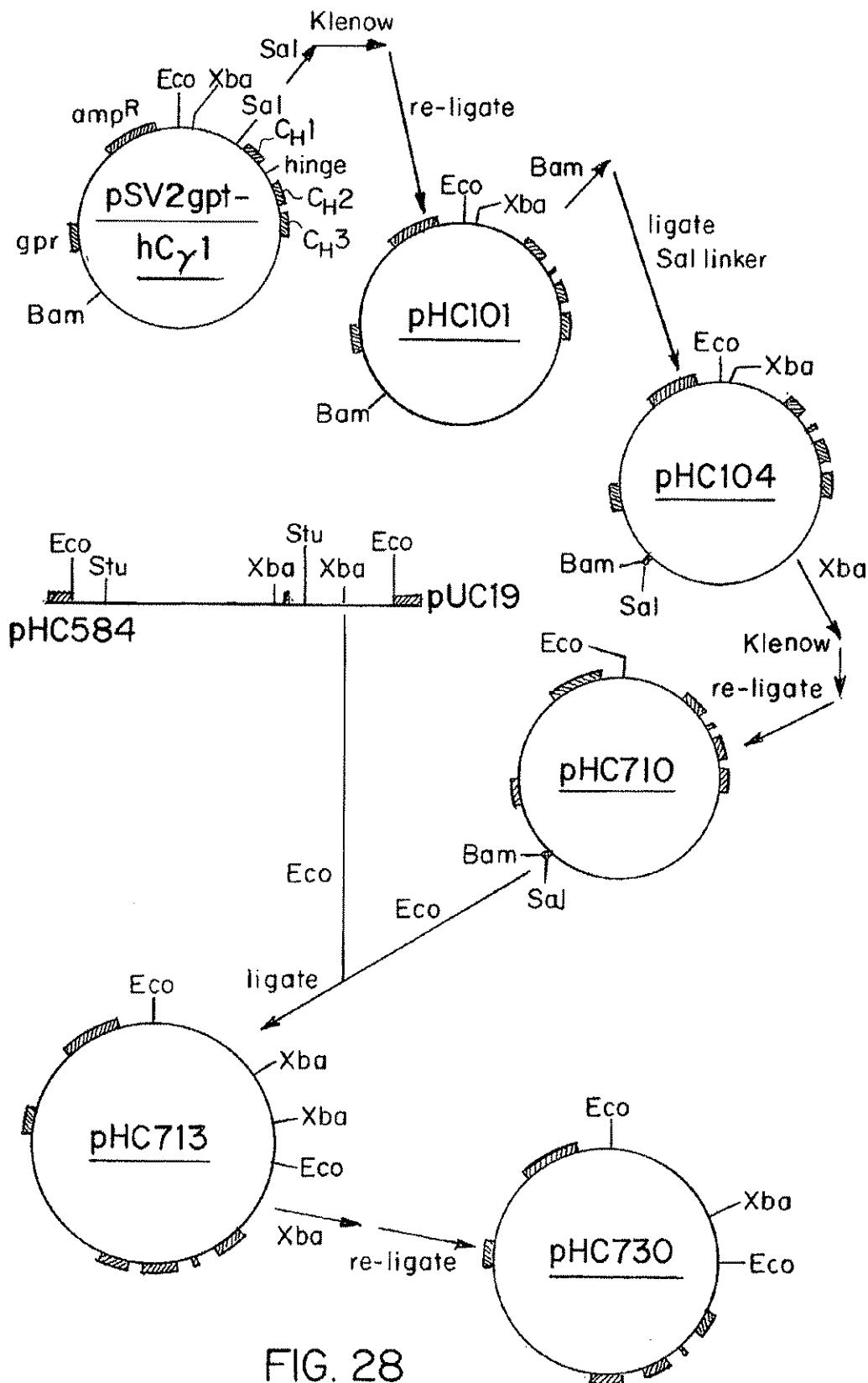


FIG. 28

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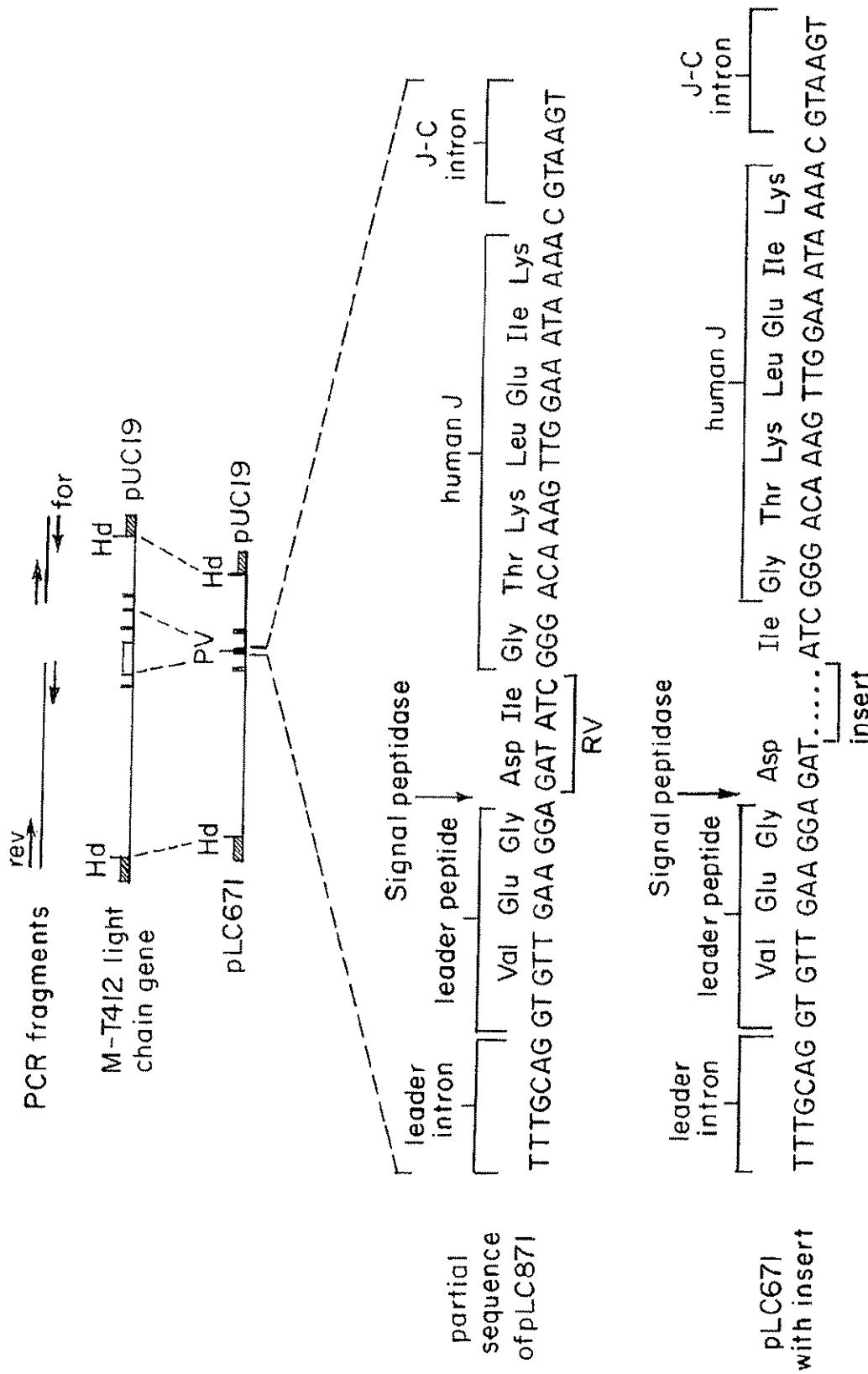


FIG. 29

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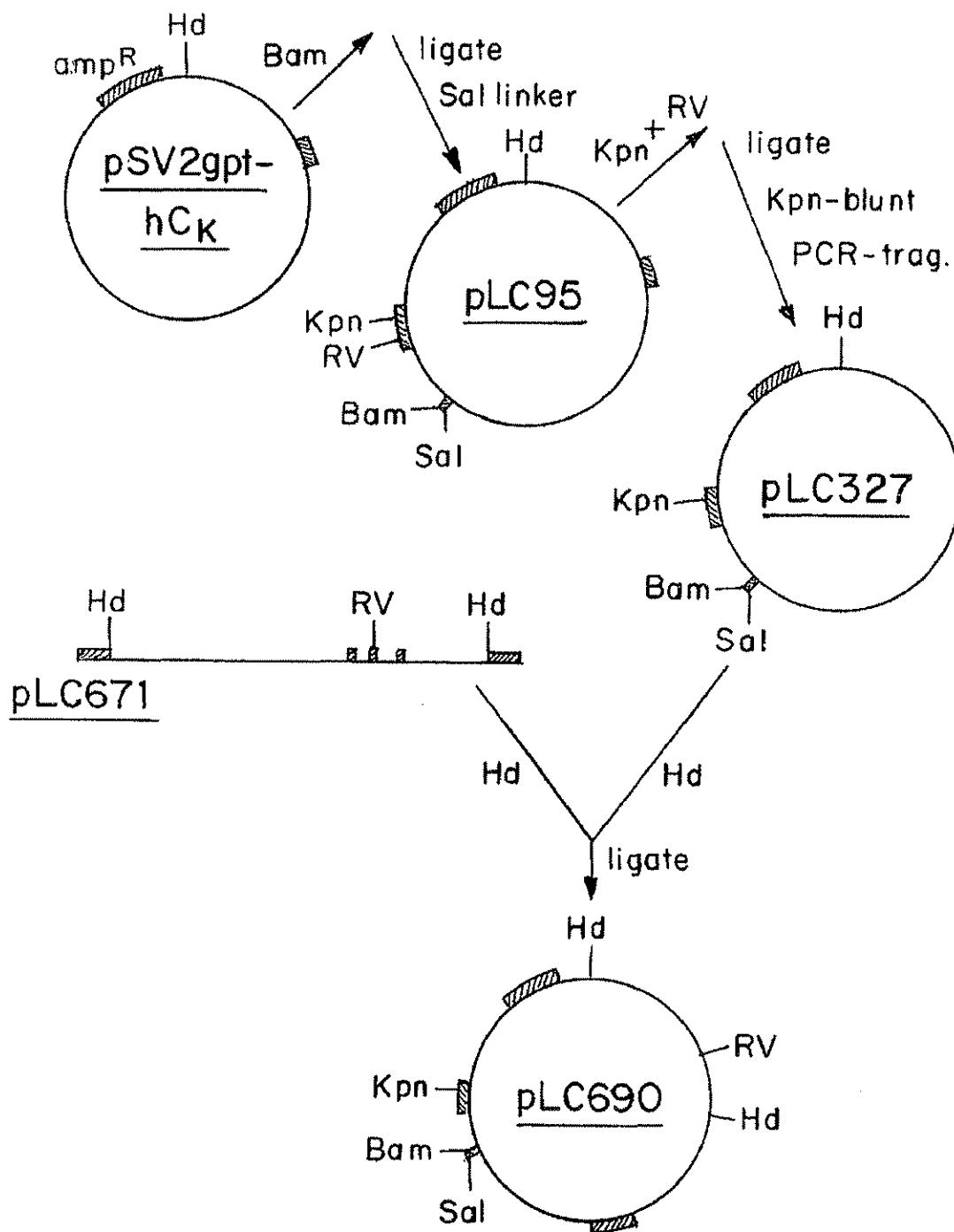


FIG. 30

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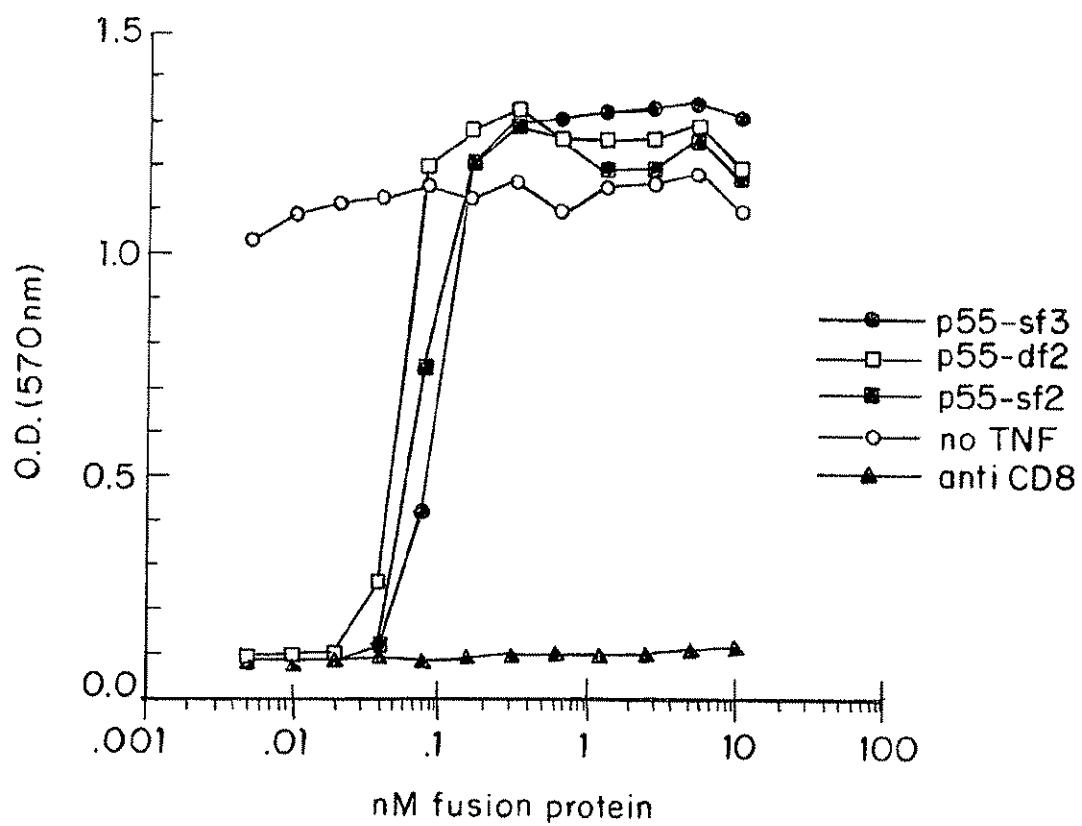


FIG. 31A